B. Remarks

The claims are 1, 2, 7-18, 20-25, 28-30 and 34, with claims 1, 2, 11, 24, and 34 being in independent form. Favourable reconsideration is respectfully requested.

Claims 1, 2, 7-18, 20-23, 28-30 and 34 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Winskill et al.* (Applied Animal Behavior Science, vol. 48, pp. 25-35 (1996)) in view of *Johnson et al.* (Equine Vet. J., vol. 30(2), pp. 139-143 (1998)), further in view of *Pagan* (Australian Equine Veterinarian, vol. 16(4), pp. 159-161 (1998)). Claims 24 and 25 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Johnson et al.*, and *Winskill et al.*, in view of *Pagan*. Applicants respectfully traverse these rejections.

The present invention provides compositions and methods by which animal stereotypy may be treated or ameliorated, or the risk of an animal developing animal stereotypy may be minimized.

Winskill does not teach or suggest any association between animal stereotypy and acidity of the intestinal tract. *Johnson* discloses that neutralising the acidity of the hindgut of horses by administering sodium carbonate to the caecum lowered the incidence of stereotypic behaviour. *Johnson* suggests that acidity in the lower gut may be a stimulus to stereotypic behaviour (page 139, right column, second paragraph, last sentence). However, *Johnson* contains no teaching or suggestion of a link between acidity in the stomach and stereotypic behaviour, nor any suggestion to provide sodium carbonate by oral administration.

The Examiner asserts that *Johnson's* feed contains stomach antacid. However, the Examiner has cited no passage in *Johnson* at which this alleged disclosure is made. At page 139, right column, second paragraph, referring to a study by Willard et al., 1977, *Johnson* states that sodium carbonate was administered to the caecum. However, there is no disclosure that

sodium carbonate is included in the feed or administered orally. Willard et al. discloses only caecal infusion of sodium carbonate, *not* oral administration. A person skilled in the art would have had no reasonable expectation that oral administration, rather than caecal infusion, of sodium carbonate would neutralise hindgut acidity. Consequently, there was no reason for a person skilled in the art to combine sodium carbonate with the feed of *Winskill* to provide an oral feed capable of performing the intended use of the composition of claims 1 and 2. Since there is no suggestion of a link between stomach acidity and stereotypy in the cited art, there was also no reason for a person skilled in the art to control stomach pH to treat or ameliorate stereotypy or to minimize the risk of development of stereotypy. These arguments, and evidence in support of the arguments, are discussed in detail below.

A person skilled in the art would not have orally administered sodium carbonate to lower the incidence of stereotypy

The Declaration of Dr. Patricia Harris, filed October 6, 2006 (hereinafter "Harris 2006 Declaration) makes it clear that a person skilled in the art would not have administered a feed composition comprising sodium carbonate to lower the incidence of stereotypy because administration of sodium carbonate by this route was not expected to reduce hindgut acidity.

The Harris 2006 Declaration discusses the state of the prior art regarding oral administration of sodium carbonate and sodium bicarbonate to horses, and provides evidence against the oral use of sodium carbonate and sodium bicarbonate to reduce hindgut acidity in the horse. In particular, the Harris 2006 Declaration refers to *Deuel* et al. (Some Physiological Effects of Sodium Bicarbonate in Diets of Yearling Horses, Proceedings of the 7th Equine Nutrition and Physiology Symposia, Virginia, USA 1981), which describes a study in which 1%

sodium bicarbonate was added to growth diets for yearling Quarter Horses. The document teaches that the pH of terminal colon digesta is similar to that of caecal contents, and that feed pH was negatively correlated with fecal pH. On this basis, Dr Harris considers that long term oral administration of sodium bicarbonate may increase, rather than decrease hindgut acidity. The Harris 2006 Declaration also refers to *Rowe* et al. (International Horse Industry Symposium, RIRDC, 2001), which teaches that buffers such as sodium bicarbonate are unlikely to reach the hindgut since the acidic conditions in the stomach convert all bicarbonate to carbon dioxide and water. The changes in pH along the digestive tract, from acidic in the stomach, to alkaline in the small intestine, to neutral/acidic in the hindgut (evidenced by *Argenzio* et al. (1974) Am. J. Physiol., vol. 226, p. 1048), and the dramatic changes in fluid volume from the stomach to the hindgut (evidenced by *Kohnke*, 1998, Feeding and Nutrition of Horses) are also cited in the Harris 2006 Declaration as evidence against the oral use of sodium bicarbonate or sodium carbonate to reduce hindgut acidity.

There was no motivation to use the antacid of *Pagan* to treat stereotypy

The Examiner asserts that a person skilled in the art would have been motivated to incorporate antacid of *Pagan* with the expectation of lowering or reducing the acidity of the hindgut. *See* Office Action, page 5, third paragraph. However, there is no disclosure in *Pagan* that inhibition of gastric acid secretion, or treatment of gastric ulcers, will lead to treatment of stereotypy. The Examiner asserts that Applicants state they cannot find any teaching in *Pagan* that associates gastric acidity with ulcers, and responds by drawing the Applicants' attention to the title of the paper by *Pagan*. Office Action, page 10, paragraph 8. The Examiner appears to have misunderstood the Applicants' response of April 30, 2008 (hereinafter the "April 30, 2008

response"), wherein it was stated on page 9 that "Applicants are unable to find any teaching or suggestion in *Pagan* that **links formation of ulcers with stereotypic behaviour**" (emphasis added). *Pagan* is concerned only with treatment of gastric ulcers in horses, not treatment of stereotypy. *Pagan* teaches that gastric acid is a major cause of gastric ulcers, and that drugs that inhibit gastric acid secretion (for example, histamine type-2 antagonists and proton pump inhibitors), and antacids that neutralise gastric acid, may be used to treat ulcers. However, there is no disclosure in *Pagan* that treatment of gastric ulcers will lead to treatment of stereotypy or cribbing.

In addition, there is no disclosure in *Pagan* that drugs that inhibit gastric acid secretion, or antacids that neutralise gastric acid, would affect hindgut acidity. Indeed, one skilled in the art would not use such compounds to affect hindgut acidity because acidity in the hindgut has a different chemical basis to stomach acidity. Evidence for this was presented in the Harris 2006 Declaration. The primary cause of stomach acidity is secretion of hydrochloric acid into the stomach, whereas abnormal acidity in the hindgut is typically caused by rapid bacterial fermentation of carbohydrate, which leads in particular to the accumulation of lactic acid (as evidenced by page 1, lines 23-29 of *Rowe* (PCT Publication No. WO 96/20709), which is already of record). Consequently, drugs that inhibit secretion of gastric acid would not affect hindgut acidity. Gastric antacids would be neutralised by the acidity of the stomach prior to reaching the hindgut. Thus, it is respectfully submitted that one skilled in the art would not have been motivated to incorporate the antacid of *Pagan* with the expectation of lowering or reducing the acidity of the hindgut.

There is no link in the cited art between stomach acidity and stereotypy

The Examiner asserts that Applicants have not provided factual evidence that there is no link between stomach acidity and stereotypy. Office Action, page 12, paragraph (v). Applicants respectfully submit that this is a rather confusing statement since the invention relates to the link between stomach acidity and stereotypy, and evidence for this is presented in the Example of the application as filed. Perhaps the Examiner means that Applicants have not provided factual evidence that there is no link between stomach acidity and stereotypy in the cited art. However, Applicants have repeatedly explained that the cited art contains no disclosure of a link between stomach (i.e. gastric) acidity and stereotypy, and evidence to support this was provided with the Harris 2006 Declaration.

At pages 8-9 of the Office Action (paragraph 7), it is alleged that Applicants argue that the Examiner arrived at associating gastric acidity with equine stereotypy by relying on an incorrect assertion that the stomach, the caecum and the hindgut are all part of the equine digestive system, and that while the shorter Oxford English Dictionary may define gastric to mean "pertaining to, or affecting the stomach", the dictionary does not say that caecum is not part of the digestive tract of the equine. Once again, the Examiner appears to be confused by Applicants' arguments presented at page 8 of the April 30, 2008 response. The caecum is of course part of the digestive tract. On page 8 of April 30, 2008 response, Applicants were pointing out to the Examiner that her allegation that "it is known in the art that gastric acidity is associated with equine stereotypy, as is evidenced in Johnson, such that treating gastric acidity would invariably treat stereotypy in the equine" is not correct. Applicants' reference to the shorter Oxford English Dictionary was to clarify to the Examiner that the term "gastric" means pertaining to, or affecting the stomach, whereas *Johnson* discloses only that it is "hypothesised

that a relationship might exist between behavioural responses and pH of the hindgut". It is common knowledge to one skilled in the art that the hindgut does not include the stomach. For example, *Rowe* (PCT Publication No. WO 96/20709) states that the hindgut (or large intestine) "consists of a colon and caecum" (page 1, lines 20-22). Merrick's Tech Information, available at www.merricks.com/digestion.html (copy attached herewith), states that the large intestine of the horse is made up of the caecum and the colon, and clearly illustrates that the stomach is separated from the large intestine (hindgut) by the small intestine.

Johnson teaches that a relationship might exist between behavioural responses and pH of the hindgut but says nothing about any relationship between stomach acidity and stereotypy. As has been explained previously, neither *Johnson* nor any other cited document discloses that stomach (i.e. gastric) acidity is associated with equine stereotypy.

The Harris 2006 Declaration makes it clear that the state of the art at the time the invention was made was that there was no link between stomach acidity and stereotypy, and that one skilled in the art would not have assumed that a link between hindgut acidity and stereotypy meant there was also a link between stomach acidity and stereotypy. In particular, the Harris 2006 Declaration clarifies that the stomach is not part of the hindgut, and that stomach and hindgut pH are not directly dependent on each other. There are dramatic changes in fluid volume as food passes from the stomach to the hindgut (evidenced by *Kohnke*), and changes in pH along the digestive system from acidic in the stomach, to alkaline in the small intestine, to neutral/acidic in the hind gut (evidenced by *Argenzio*). Acidity in the hindgut has a different chemical basis to stomach acidity. Accordingly, it is respectfully submitted that there is no disclosure in the cited art that would lead one skilled in the art to believe that there is a link between stomach acidity and stereotypy.

Future intended use of the claimed compositions

At paragraph (e) on page 9 of the Office Action, the Examiner appears to acknowledge that it was not previously disclosed that gastric acidity is associated with equine stereotypy. However, the Examiner comments that claims 1 and 2 are directed to compositions that have the future intended use of treatment, amelioration, or minimizing the risk of development of stereotypy, and that the cited art composition would be capable of performing the recited intended use.

As acknowledged by the Examiner, *Winskill* does not teach a feed composition that contains an antacid (see page 3 of the Office Action), and the combined teaching of *Johnson* and *Winskill* does not teach administering proton pump inhibitor or histamine type-2 antagonist to control stomach pH (see pages 4-5 of the Office Action).

As explained above and in several of Applicants' previous responses, one skilled in the art could have had no reasonable expectation that oral administration of sodium carbonate would reduce hindgut acidity. Consequently, one skilled in the art would not have been motivated to combine sodium carbonate with the feed of *Winskill* to achieve the result of an oral feed composition (or a pharmaceutical composition) for use in the treatment or amelioration of animal stereotypy, or for minimizing the risk of an animal developing animal stereotypy. Therefore, Applicants respectfully submit that the claimed compositions are patentable over the cited art.

Harris Declaration filed April 30, 2008

At pages 10-12 of the Office Action, the Examiner asserts that the Declaration of Dr. Harris filed April 30, 2008 (hereinafter the "Harris 2008 Declaration") is not sufficient to

overcome the rejection of claims 1, 2, 7-18, 20-25, 28-30 and 34. The Examiner further asserts that the evidence provided by Applicants on October 11, 2006 would not have led the artisan away from including sodium carbonate in a feed for horses, and that the Harris 2006 Declaration supports oral administration of sodium carbonate or the obvious addition of sodium carbonate to the feed of *Winskill* to reduce stall-walking/stereotypy. Office Action, page 12, paragraph (vi). Applicants are confused by the Examiner's assertions. The Harris 2006 Declaration does *not* support oral administration of sodium carbonate or the obvious addition of sodium carbonate to the feed of *Winskill* to reduce stall-walking/stereotypy. In fact, the Harris 2006 Declaration specifically refers to evidence as to why one skilled in the art would *not* have orally administered sodium carbonate in a section entitled "Evidence against oral use of sodium carbonate and sodium bicarbonate to reduce hindgut acidity in the horse". Pages 3-4 of the Harris 2006 Declaration. Applicants have explained in detail above, and in several previous responses, that one skilled in the art would have had no reasonable expectation that addition of sodium carbonate to the feed of *Winskill* would have any effect on stereotypic behaviour.

Evidence that the cited art teaches away from the claimed invention

As explained above and in prior Office Action responses and based on the evidence provided in the Harris 2006 Declaration, it is clear that the cited art teaches away from oral administration of sodium carbonate to horses to reduce hindgut acidity. Applicants have also presented evidence that there was no link between stomach acidity and stereotypy in the cited art, and that one skilled in the art would not have assumed that a link between hindgut acidity and stereotypy meant there was also a link between stomach acidity and stereotypy.

Since there is no link between stomach (i.e. gastric) acidity and stereotypy in the cited art, one skilled in the art would have had no reason to reduce stomach acidity to treat stereotypy. The skilled person would not have administered the gastric antacids disclosed in *Pagan* to reduce hindgut acidity because they would have had no expectation that such antacids would affect hindgut acidity. Evidence for this was provided in the Harris 2006 Declaration. In particular, the primary cause of stomach acidity is secretion of hydrochloric acid into the stomach, whereas abnormal acidity in the hindgut is typically caused by rapid bacterial fermentation of carbohydrate, which leads in particular to the accumulation of lactic acid (as evidenced by *Rowe* PCT Publication No. WO 96/20709, page 1, lines 23-29). Consequently, drugs that inhibit secretion of gastric acid would not affect hindgut acidity. Gastric antacids would be neutralised by the acidity of the stomach prior to reaching the hindgut. Thus, one skilled in the art would have had no motivation to combine *Pagan* with *Winskill* and *Johnson*. The Examiner has not provided the requisite reason to combine the cited references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

In addition, the Harris 2006 Declaration describes how the cited art taught away from oral administration of sodium carbonate, from administration of gastric antacids to reduce hindgut acidity, and that there was no link between stomach acidity and stereotypy. Evidence in a Declaration must be considered by the Examiner. *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007) (vacating PTO decision as the PTO improperly failed to consider applicant's rebuttal evidence).

In addition, the PTO must also consider evidence related to secondary considerations in connection with the determination of obviousness. *Id.*

Evidence of unexpected results

Evidence of unexpected results was presented in the Example of the present application. A first group of crib-biting and control foals were administered a typical base diet supplemented with forage. A second group of crib-biting and control foals were administered a composition of the invention, comprising the same diet as the first group but also including stomach antacid. The relationship between stomach condition and crib-biting behaviour was examined by comparing the extent to which crib-biting changed over the course of the trial with change in stomach condition. It was found that foals administered a composition of the invention showed a resolution of mild ulceration, and foals whose mild ulceration cleared showed the greatest improvement in crib-biting. It was concluded that an improvement in stomach condition was associated with reduced crib-biting behaviour.

The cited art had suggested only a link between hindgut acidity and stereotypy. The results presented in the application are surprising and, as explained at page 17 of the specification, demonstrate for the first time a relationship between stomach condition and abnormal oral behaviour in the horse.

Long-felt but unresolved need

As explained at pages 1-2 of the specification, at the time of the invention the cause or causes of stereotypies were not known, and this lack of knowledge severely hampered the development of effective treatments and preventatives for stereotypies. It is also explained that use of stable toys was not found to be an effective way of preventing equine stereotypy, physical prevention is not successful because the animal still has the urge to perform the behaviour, and preventatives such as social isolation, collar fitting, aversion therapy and surgery

are undesirable. In addition, as stated at page 4 of the specification, there was, therefore, an urgent need to provide effective treatments, preventatives or ameliorative for stereotypy which do not involve any undesirable practices being performed on an animal being treated.

Further evidence for this long-felt, but unresolved need is provided in Winskill et al., "Stereotypies in the stabled horse: Causes, treatments and prevention", Current Science, vol. 69, no. 4, pp. 310-316 (1995), which is already of record. At page 311, it is stated that, "Quantitative evidence relating to the causal factors of stereotypies in stabled horses is very scarce in the scientific literature, the majority being purely anecdotal in nature …. This lack of evidence implies that the causes of abnormal behaviour are still unclear, and more research is still required." The document further states, at pages 313-314, that, "Traditionally, the control of crib-biting and wind-sucking has been directed towards preventing the behaviour by mechanical or surgical techniques … Attempts such as surgery or the use of a cribbing strap when used to prevent the performance of a behaviour prevent only its manifestation without eliminating the causal factors involved. Such measures may cause additional frustration for the animal, which may perform another stereotypic behaviour that it is not restricted from expressing, further compromising its welfare. … However, in their most severe forms, wind-sucking and crib-biting may continue to be performed when turned out to pasture. … In such circumstances where the behaviour continues despite recommended changes in feeding and other management practices, such as the provision of social companionship and increased exercise regimes, the use of narcotic antagonist drugs such as naloxone and naltrexone, may play a role, although this could be argued by some to be no better than surgery or physical restriction." The methods and compositions of the present invention are believed to treat a cause of stereotypy, and do not involve any undesirable practices being performed on the animal being treated.

Wherefore, it is respectfully submitted that the presently claimed invention is not disclosed or suggested by the art of record whether taken alone or together. Accordingly, it is respectfully requested that the claims be allowed and the case passed to issue.

Applicants' undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

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